Lipid Catabolism

Introduction

Lipid catabolism is done during the **glucagon-dominant** state between feedings. Once the dietary glucose runs out, insulin will fall, and glucagon will rise. Never can lipid synthesis (insulin dominant) and lipid catabolism (glucagon dominant) occur at the same time. This is ensured by the hormone state and by substrate-level regulation in the various tissues, as well as the compartments in which they occur. Lipid synthesis occurs in the cytoplasm, lipid catabolism in the mitochondria. Lipid catabolism can be conducted by **muscle**, **adipose**, and **liver**. Red blood cells have no mitochondria, so can't do anything related to lipids.

Because fatty acids are lipophilic, they pass freely between lipid bilayers. This means that we'll need to do something special to fatty acids to ensure that they stay in the mitochondria. It will also make sense that substrates of synthesis inhibit enzymes of catabolism, and substrates of catabolism inhibit enzymes of synthesis. In this lesson we'll explore **mobilization of fatty acids** from **adipose**, **activation** of fatty acids in the intermembrane space of mitochondria, β **oxidation** of fatty acids in the mitochondria, and the **regulation** of this system and how it interacts with the insulin-dominant state. We then close with a special pathway for odd-chain fatty acids called the **propionic acid pathway**.

Mobilization of Fatty Acids from Adipose

Adipose cells use glucose from the insulin-dominant state to make glycerol-3-phosphate, which takes the fatty acids from the liver during the insulin-dominant state to store fatty acids as triglycerides. Insulin promotes lipoprotein lipase to get the fatty acids into the adipose; insulin stimulates the uptake of glucose, and the formation of triglycerides.

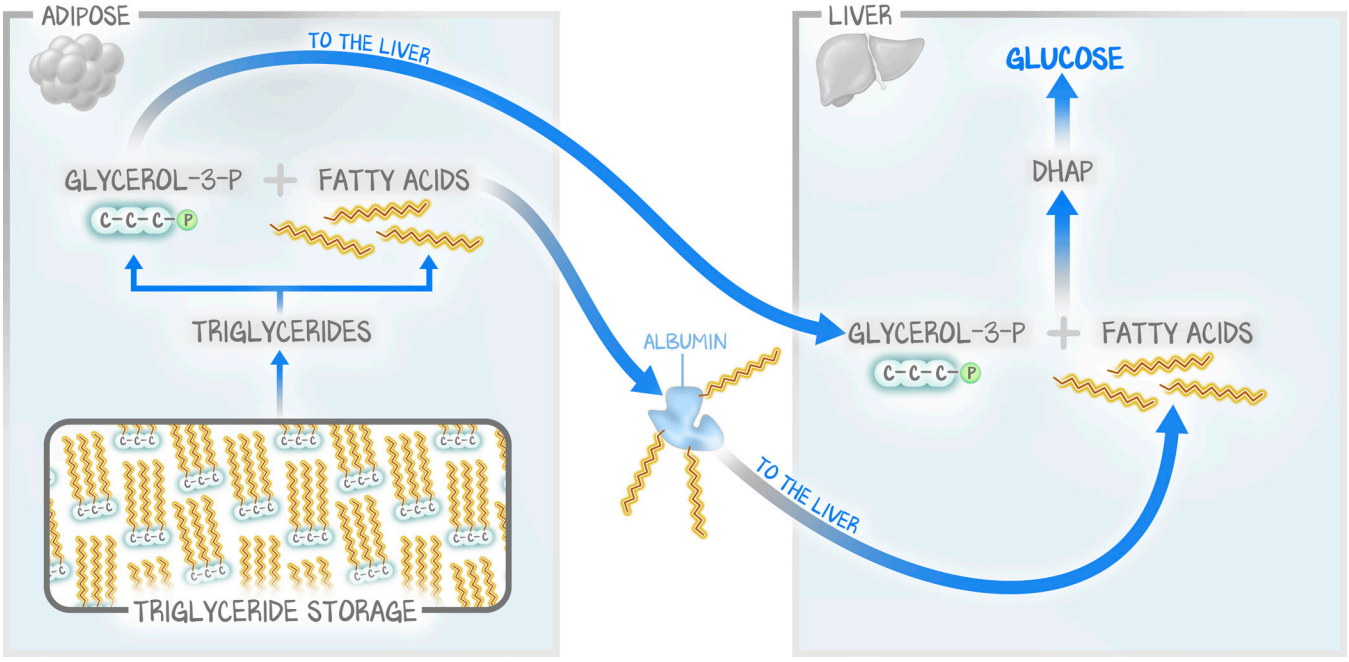

Figure 15.1: Mobilization of Triglycerides from Adipose in the Glucagon-Dominant State
In the glucagon-dominant state, assembled triglycerides are disassembled into glycerol and fatty acids, and the pieces are sent back to the liver.

Now, in the glucagon-dominant state, the stored triglycerides need to be mobilized to their parts for transport back to the liver. **Hormone-sensitive lipase** is a lipase within the adipose cell. Its activity increases as insulin levels fall and is stimulated by epinephrine, glucagon, and cortisol. Adipose has no glucagon receptor, so it is **predominantly the low insulin levels** that stimulate hormone-sensitive lipase. In other words, it is a poorly named enzyme.

This creates **fatty acids** which, bound to **albumin**, go to the liver. There's no need for a specialized apoprotein for the reverse trip; no need for a "from" or "destination" tag. This also creates **glycerol**, which returns to the liver. Remember that the liver-based glycerol returned already after lipoprotein lipase took the fatty acids. This glycerol is made by adipose tissue from glucose and is also being sent back to the liver.

Glycerol in the Liver

Glycerol is able to be converted into **DHAP** in an intermediate step of glycolysis. In the glucagon-dominant state, **gluconeogenesis** is on, glycolysis off. That glycerol, via DHAP, is converted to **glucose**. In a sense, the adipose tissue sends the liver the materials the liver needs to make glucose (glycerol) and the materials to generate ATP in the liver (fatty acids) at the exact time when it is supposed to be making glucose for the rest of the body.

Fatty Acids in the Liver: Activation

Fatty acids returning on albumin are sent to the mitochondria. Don't worry about the mechanics of "from adipose to mitochondria in the liver." When the fatty acids arrive in the **intermembrane space** (the same place hydrogen ions are pumped for the electron transport chain), they are **activated**. Remember, activation of a fatty acid involves adding a CoA. **Fatty acyl-CoA synthetase** harnesses the power of **ATP** to activate (attach a CoA to) the fatty acid. This activating step does cost energy. Activating, charging the fatty acid, also makes it unfriendly to lipid bilayers.

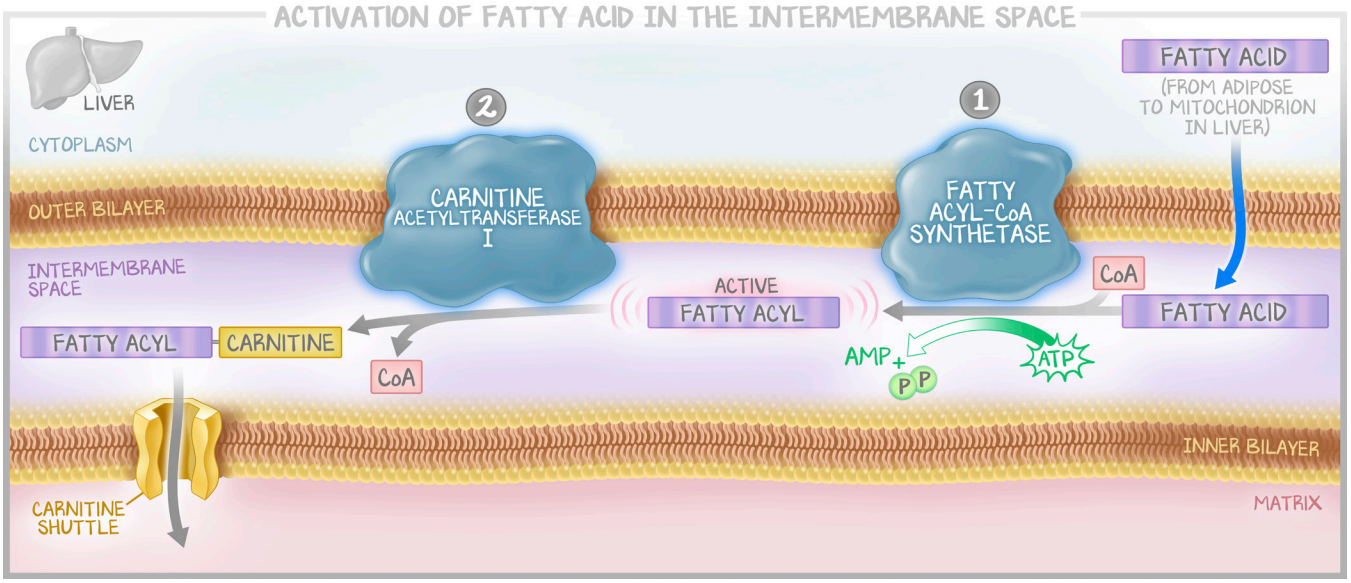

Figure 15.2: Activation of Fatty Acid in the Intermembrane Space
Activation of the fatty acid by CoA ensures that the newly arrived fatty acid stays in the mitochondrial compartment. Addition of carintine ensures that travel of trapped fatty acid is toward the matrix.

This means that once the CoA is attached, the fatty acid can't leave the intermembrane space. This ensures that fatty acids bound for oxidation, during catabolism, aren't sent to the cytoplasm where they can be utilized in synthesis. This also means that to get the fatty acyl-CoA to the mitochondrial matrix from the intermembrane space for oxidation, a **shuttle** is needed—the **carnitine shuttle**.

Activation ends with the second enzyme, **carnitine acyltransferase-1**. This simply swaps the energy of the CoA for the energy and shape of carnitine. This process will need to be reversed on the other side of the shuttle. Fatty acyl-carnitine is moved from the intermembrane space to the mitochondria via the **carnitine shuttle**.

Fatty Acids in the Liver: Oxidation

The first step is reversal of the carnitine back to an activated fatty acid with CoA by **carnitine acetyltransferase-2**. This is the exact opposite of carnitine acetyltransferase-1 and no energy is required for either step. This releases the carnitine to move more fatty acids through the carnitine shuttle. The CALT-1-shuttle-CALT-2 sequence ensures that the fatty acyl-CoA is both activated (the CoA) and moved to the correct location (the mitochondrial matrix).

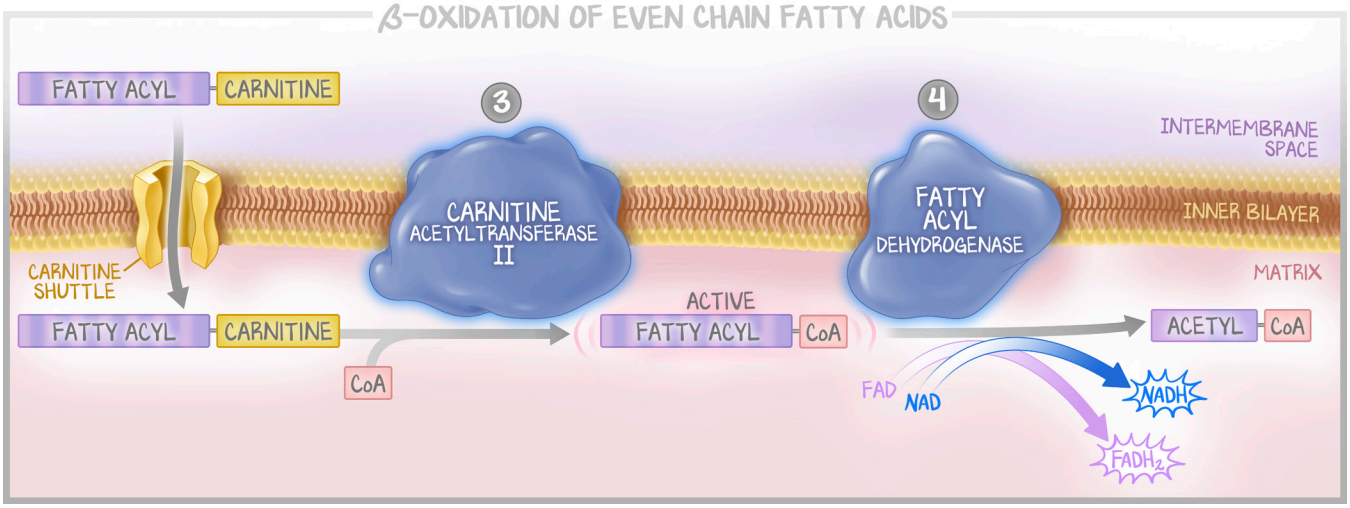

Figure 15.3: β oxidation of Even-Chain Fatty Acids
β oxidation occurs within the mitochondrial matrix, first releasing carnitine to shuttle the next fatty acid through, then secondly removing carbons, one acetyl-CoA at a time, generating high-energy compounds.

The process by which fatty acids are catabolized and turned into energy is through **fatty acyl-CoA dehydrogenase**. You'll recognize "dehydrogenase" as "the thing that makes NADH and $FADH_2$." And indeed it does. **Every cycle of fatty acyl-CoA dehydrogenase** produces an **NADH** and an **$FADH_2$**. Because oxidation occurs in the mitochondria, these compounds are sent directly to the electron transport chain for ATP generation. **Every cycle** of fatty acyl-CoA dehydrogenase removes **two carbons** from the fatty acid chain, in the form of **acetyl-CoA**. This is exactly the opposite of the fatty acid synthase of lipid synthesis.

We say "every cycle" because fatty acyl-CoA dehydrogenase will do one cycle for every two carbons on a fatty acid chain. Technically, there is one enzyme that does **long-chain acyl-CoA dehydrogenase** (LCAD, > 10 carbons) and another enzyme that does **medium-chain acyl-CoA dehydrogenase** (MCAD, < 10 carbons). But they both work the same way, each making an acetyl-CoA and generating the same energy (NADH and $FADH_2$). They take a long strand of carbons, remove one acetyl-CoA, and harness the energy stored in fatty acid synthesis.

This is the reverse of fatty acid synthase but poses the same energy issue. Sixteen carbons are in palmitate, accounting for eight acetyl-CoA, but it allows for only **seven** cycles to decompose.

Fatty Acids in the Liver: Propionic Acid Pathway

Since MCAD and LCAD remove **two carbons every cycle**, they work nicely when fatty acid gets broken down. Since palmitic acid (16 carbons) is an even carbon, and it's the only one we know how to make from scratch, it makes sense that our default catabolic pathway is two carbons at a time. But what happens when we eat a fat with an odd number of carbons? **Everything is identical except for the final round**.

The body is really good at removing an acetyl-CoA. With an odd number of carbons on a chain, two carbons can be removed at a time, indefinitely—until the end, when there are **three left**. Remove an acetyl-CoA and, in theory, there would be two acetyl-CoA left. But one acetyl-CoA taken from a 3-carbon structure leaves behind a 1-carbon structure. The pathway developed to address this is the **propionic acid pathway**.

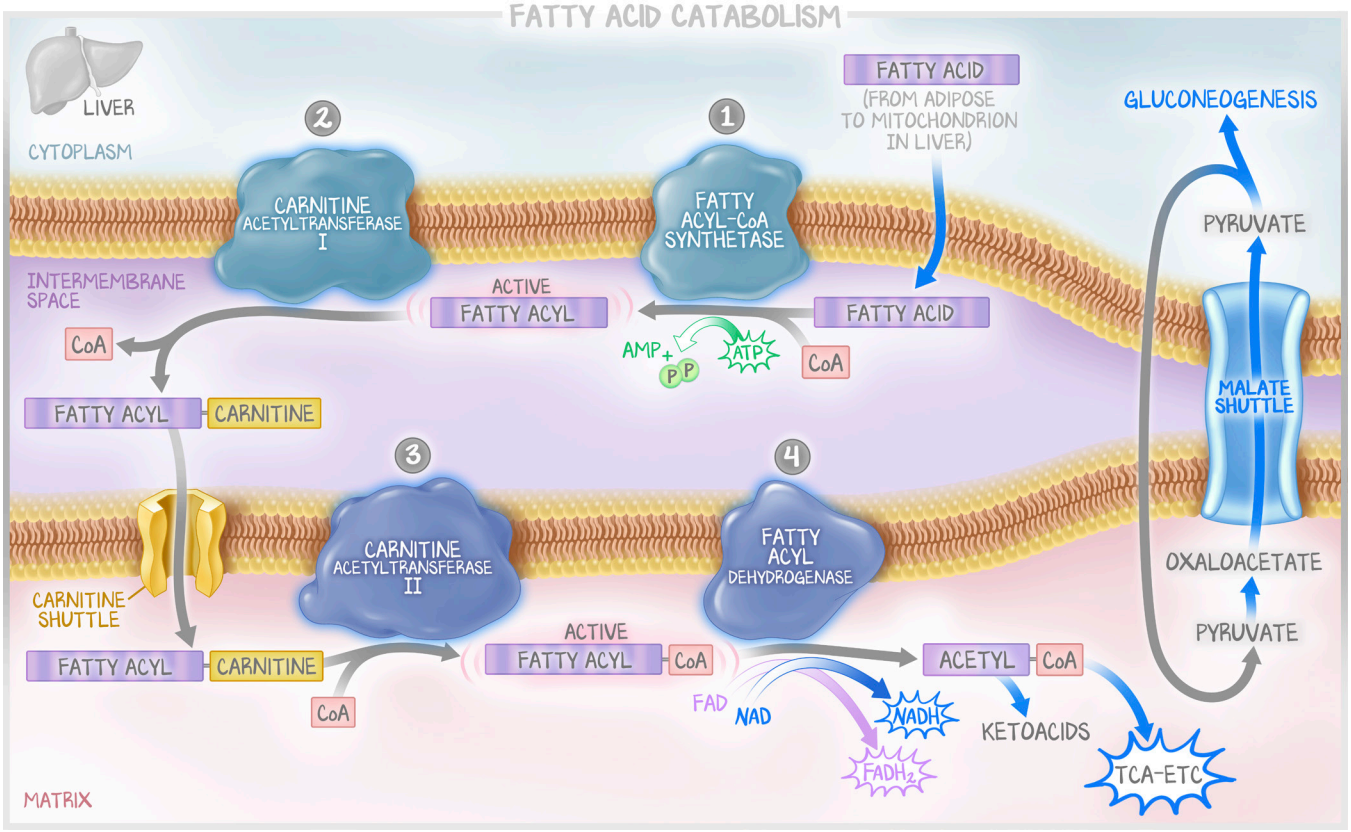

Figure 15.4: Fatty Acid Catabolism
The complete picture in relation to using fatty acids to produce energy.

The 3-carbon fatty acid is **propionyl-CoA**. Propionyl-CoA (3 carbons) with a carbon added by **propionyl-CoA carboxylase** results in **methylmalonyl-CoA**, a 4-carbon structure. Using a methylmalonic-CoA mutase, methylmalonyl-CoA acid is transformed into succinyl-CoA. **Succinyl-CoA** is in the Krebs cycle, which can be used to run TCA-ETC, or it can be removed from the cycle to make glucose. In this sense, **odd-chain fatty acids can contribute to gluconeogenesis** (the final product being succinyl-CoA), whereas the even-chain fatty acids can only become acetyl-CoA. Notice also

we didn't go from a 3-carbon to a 4-carbon and just do a usual reaction; we went from a 3-carbon to a 4-carbon, then to its own thing.

The propionic acid pathway is useful because of its enzymes. The carboxylase requires biotin, niacin, and riboflavin to work. Most importantly, **methylmalonyl-CoA mutase requires B_{12}**. In a patient with a B_{12} deficiency, there'll be an accumulation of **methylmalonic acid**. Since folate is nowhere involved in this process, there won't be any change in methylmalonic acid in a low or normal folate state. Both cause megaloblastic anemia. An elevation of methylmalonic acid, therefore, separates B_{12} from folate deficiency. B_{12} deficiency causes neural changes as well as anemia, whereas folate deficiency causes only anemia. It should be clear that **fatty acid catabolism** is the difference. Excess methylmalonic acid causes deposition in myelin sheets, leading to loss of proprioception in the dorsal column's medial lemniscus system.

MCAD Deficiency

Fatty acid catabolism provides the energy for the liver to maintain its high-energy state even in the glucagon-dominant state. The $FADH_2$ and NADH produced by LCAD and MCAD get turned into ATP. The acetyl-CoA produced by LCAD and MCAD enter the TCA and generate even more ATP. If LCAD were working, but there were a defect of MCAD, **long-chain fatty acids could still be metabolized**, but then **medium-chain fatty acids could not**. That would mean that (roughly) half of the energy stored in fatty acids could not be accessed. That means the liver would have a hard time doing what it is supposed to do. It wouldn't have the energy for gluconeogenesis, so there would be **fasting hypoglycemia**. But MCAD deficiency means there would be a paucity of acetyl-CoA. All acetyl-CoA made by LCAD would go toward TCA-ETC to give the liver the energy it needed. That means there would be **no ketogenesis**. The presence of **hypoglycemia AND no keto acids** means there must be a defect in fatty acid catabolism. If the hypoglycemia were from something else (von Gierke disease, for example), with fatty acid catabolism intact, the backup energy source, the keto acids, would still work. This can be identified **early in life** (first 6 months) and presents as **lethargy**, **coma**, **hypoglycemia**, and **low ketones**. Symptoms can be provoked by an **overnight fast**. Measuring levels of fatty acid in the blood reveals **massively increased fatty acids 8-carbons and 10-carbons long**. The disease can be treated with frequent feeding on a high-carbohydrate, low-fat diet. The incidence is 1 in 10,000 and is the **most common inborn error of metabolism**. The symptoms will flare under stress—periods of fasting or infection when additional resources are required.

Myopathic Carnitine Acyltransferase Deficiency

Clear parallels exist between myopathic carnitine acyltransferase deficiency and McArdle's disease, which is a deficiency found only within muscle cells. In McArdle's disease, the muscle can't access glycogen. This means a relative hypoglycemic state in an actively exercising muscle. This results in weakness, pain, and muscle breakdown during exercise. A muscle in this state shows an accumulation of sugar granules.

In myopathic carnitine acyltransferase deficiency, the muscles are unable to burn fatty acids. That is the same thing as "can't access glucose," in terms of energy. Either way, between meals there is insufficient energy for the muscle to exercise. In the **autosomal recessive** variant of CAT deficiency in the muscle, the lack of energy means **weakness**, **pain**, and **muscle breakdown** (myoglobinuria) with exercise. Like McArdle's disease, it presents in **adolescence or early adulthood**. When biopsied, rather than sugar granules as in McArdle's, there will instead be deposits of **fatty acids**, as activated fatty acids accumulate in mitochondria.

LCAD Deficiency and Systemic Carnitine Acyltransferase Deficiencies Are Incompatible with Life

Dead patients don't require treatment or diagnosis.